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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/769,902	01/25/2001	Reba Goodman	61545/JPW/RAD	5006

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EXAMINER	
PAPPU, SITA S	
ART UNIT	**PAPER NUMBER**
1636	16

DATE MAILED: 07/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/769,902	Applicant(s) GOODMAN ET AL.	
	Examiner Sita S Pappu	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The non-responsive letter (paper #8) mailed 05/20/2002 is hereby withdrawn and an action on the merits follows.

Claims 1-12 are pending in the instant application. This paper contains an examination of claims 1-12 on their merits.

Specification

The disclosure is objected to because of the following informalities:

The specification has improper references to figures. The Office of Petitions (Paper # 4, 07/27/2001) required an amendment to the specification cancelling all reference to Drawings and/or Figures, when the filing date of 01/25/2001 was granted on the petition filed by the Applicant. Appropriate correction is required in response to this Office Action. See MPEP 601.01(g).

Double Patenting

Applicant is advised that should claims 1, 2, 5, and 8 be found allowable, claims 9, 10, 11, and 12 will be objected to under 37 CFR 1.75 as being substantial duplicates, respectively, thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

In the instant case, claims 1 and 9 are both drawn to a noninvasive method for gene regulation and have identical scope.

Claims 2 and 10 are both drawn to the use of nCTCTn sequences in an HSP70 gene promoter as the electromagnetic field response elements and have identical scope.

Claims 5 and 11 are both drawn to the use of nCTCTn sequences in a c-myc gene promoter as the electromagnetic field response elements and have identical scope.

Claims 8 and 12 are both drawn to the application of electromagnetic field at a field strength of about 8μT and a frequency of about 60Hz for a time of about 30 minutes and have identical scope.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided

by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the Invention and Breadth of the Claims:

Claims 1-12 are directed to a method of gene regulation during gene therapy by introducing electromagnetic field response elements into a gene promoter and applying an electromagnetic field to the introduced electromagnetic filed response elements to induce gene expression, wherein the electromagnetic field response elements are nCTCTn sequences in c-myc promoter or hsp70 promoter. Therefore, the nature of the invention is directed toward gene therapy using electromagnetic field to induce expression of exogenous nucleic acids during gene therapy.

The claims encompass a method of gene regulation during gene therapy and expression of an exogenous nucleic acid in the cell of an organism in vivo, through the application of electromagnetic field, and thereby cover all organisms including human beings. The claims encompass gene therapy, because the only purpose of the delivery and expression of an exogenous nucleic acid, as disclosed by the specification, is for therapeutic purposes, the claims have a very broad scope, and are not limited to the simple delivery and expression of the exogenous nucleic acids in vitro. The specification does not disclose any other purpose or utility for the method of the instant invention. Thus, the claims encompass the application of the said method to the whole organism for the purpose of gene therapy and have a very broad scope.

State of the art:

At the time of filing, *in vivo* gene therapy utilizing the direct administration of recombinant nucleic acids, whether in the form of retroviruses, adenoviruses, or plasmid DNA/liposome complexes, was considered to be highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery..", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Science, Vol. 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, " difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1).

Orkin et al. further states in a report to the NIH that, " .. none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", and that," [w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol" (Orkin et al. (1995) "Report and recommendations of the panel to assess the NIH investment in research on gene therapy", page 1, paragraph 3, and page 8, paragraph 2).

Among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are anti-viral immune responses, particularly against adenoviral proteins, and the identity of the promoter used to drive gene expression.

Verma et al. teaches that weak promoters produce only low levels of protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein expression be achieved (Verma et al., *supra*, page 240, column 2). Verma et al. further warns that, " .. the search for such combinations is a case of trial and error for a given type of cell" (Verma et al., *supra*, page 240, bridging sentence of columns 2-3). The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al. Human gene Therapy, vol. 7, pages 1781-1790, September 1996, see page 1789, column 1, first paragraph).

Further, Jin et al. (1997, Bioelectrochem Bioenerg. Vol. 44, No.1, pages 111-120) teach that efficiency of induction is dependent on the type of cells and the source of cells exposed to the electromagnetic fields (page 112, bridging paragraph of the columns) and same cells from different sources have significantly different cellular morphology, growth characteristics, and responses to TPA and that differences in reactivity are sufficient to result in differences in transcript levels. Thus, the art at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect *in vivo* by expressing a therapeutic gene using any of the expression constructs known in the art at the time of filing was extremely low.

Amount of Direction provided and existence of working examples:

The prior art teaches a method of gene regulation in vitro in cell lines using the electromagnetic field response elements, nCTCTn, from c-myc promoter and hsp70 promoter at field strength of 8μT and 60 Hz. However, prior art does not teach the use

of the method for the purpose of gene therapy in whole organisms. Prior art does not teach the usefulness of the method to such levels that a therapeutic effect is obtained. In cases where prior art does not teach how to use the method, all the guidance for practicing the invention must come from the specification. The specification fails to disclose how long the induced expression of exogenous nucleic acids in the cells of organisms lasts, and whether it is long enough to see a therapeutic effect.

The specification teaches the use of the EMREs from c-myc promoter placed upstream of CAT or luciferase reporter constructs that were otherwise unresponsive to EM fields (page 17, line 9), transfection of the HeLa cells with the constructs and exposure to EM fields and teaches significant increases in CAT and luciferase activity in the protein extracts of EM field-exposed transfectants. The specification, however, does not provide any guidance on how this increased activity was measured or quantified in terms of the usefuleness of the method for gene therapy and for how long after transfection this effect was observed, and whether repeat inductions were necessary and if so, how frequently they were needed, and the level of gene expression needed to achieve a therapeutic result, such that one of skill in the art would accept that their method would result in a therapeutic outcome and be able to practice the method using the guidance provided in the specification.

The specification does not provide guidance to overcome the art recognized unpredictabilities of gene therapy because it lacks correlative evidence between the delivery and expression of a gene and any therapeutic effect. While the specification demonstrates the transfection of cell lines in vitro using the method of the instant

invention, it is not predictable that the results obtained in vitro correlate to results expected in vivo such that one of skill would have reasonable expectation of obtaining therapeutic levels of expression of any gene of interest. It would require undue experimentation on the part of a skilled artisan to determine the vector, the dosage, frequency and route of administration, to obtain a level of expression that would result in a therapeutic effect.

Predictability of the Art, Amount of Experimentation and Skill level of the artisan:

While it is relatively routine in the gene transfer art to achieve expression at non therapeutic levels, i.e., expression at low levels or at levels providing no patentably useful phenotypic effect, it is unpredictable without specific guidance and direction whether one will definitively achieve expression of a particular molecule at levels sufficient for a therapeutic effect. Thus, when there is deficiency in the art in terms of predictability of obtaining therapeutic levels of expression, the Applicant must provide sufficient guidance and direction which demonstrates or reasonably correlates to therapeutic levels of expression of a DNA product in an art recognized animal model or patient as claimed.

Although the skill of an artisan in this subject area is considered to be very high, it would require undue experimentation on the part of an artisan to make and use the invention as specified and use the invention as claimed. The specification and the working examples do not provide sufficient guidance to practice the invention as claimed. Therefore, in the absence of specific guidance and working examples, the use of the claimed method in gene therapy is unpredictable. In such a situation, one skilled

in the art would not know how to use the invention as claimed, without undue experimentation. In view of the limited guidance in the specification, and limited working examples, and the unpredictability of the art, one skilled in the art would be required to engage in undue experimentation, in order to use the invention.

Thus, due to the art recognized unpredictability of achieving therapeutic levels of gene expression following direct or indirect administration of nucleic acids, the lack of guidance provided by the specification for the parameters affecting delivery and expression of therapeutic amounts of DNA into the cells using electromagnetic field induction, the lack of guidance concerning the treatment of any disease using the claimed method of the instant invention, it would have required undue experimentation to practice the instant invention and the skilled artisan would not have predicted success in using the claimed method of transfection and expression via electromagnetic field induction for the purpose of gene therapy. Thus the specification does not enable one skilled in the art to use the claimed invention in gene therapy.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 9 are indefinite in that the preamble recites gene therapy but there is no step for introducing the constructs into an animal and expressing an exogenous

gene in the animal. Claims 2-8 and 10-12 are rejected insofar as they depend from claims 1 and 9.

Claim 3 is indefinite in its recitation of "a number of the nCTCTn sequences is 3". There is no antecedent basis for "a number of the nCTCTn sequences". Claim 4 is rejected insofar as it depends from claim 3.

Claim 6 s indefinite in its recitation of "a number of the nCTCTn sequences is 8. There is no antecedent basis for "a number of the nCTCTn sequences". Claim 7is rejected insofar as it depends from claim 6.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-12 are rejected under 35 U.S.C. 102(a) as being anticipated by Lin et al. (2001, Journal of Cellular Biochemistry vol. 81, pages 143-148. Published online in Wiley Interscience, December 2000).

Although the method of the invention is not enabled for gene therapy, the method itself and the EMRE elements from c-myc promoter and hsp70 promoter are disclosed in the prior art. And the claims do not require that the constructs be introduced into an animal.

Lin et al. teach the use of nCTCTn sequences from c-myc promoter and hsp70 promoter in gene regulation (see abstract, page 143). In particular, Lin et al. teach the use of eight nCTCTn elements from c-myc gene promoter (page 143, right column, first paragraph) placed upstream of CAT or luciferase constructs that were otherwise unresponsive to EM fields (page 143, right column, bottom paragraph) in HeLa cells exposed to 8μT and 60 Hz fields. Lin et al. further teach the use of three nCTCTn binding sites from hsp70 promoter and the three nCTCTn sequences from the hsp70 promoter used lie between –230 and –160 (page 143, left column, line 9-12).

The 900 bp region of c-myc gene promoter used contains eight copies of nCTCTn and extends from –353 to –1257 (page 144, left column, "materials and methods", second paragraph).

Thus, Lin et al. (2001) anticipated the invention of claims 1-12.

Claims 1, 5-8, 9, 11, 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Lin et al. (1994, Journal of Cellular Biochemistry vol. 54, pages 281-288).

Although the method of the invention is not enabled for gene therapy, the method itself and the EMRE elements from c-myc promoter and hsp70 promoter are disclosed in the prior art. And the claims do not require that the constructs be introduced into an animal.

Lin et al. (1994) teach a method of gene regulation by exposing c-myc gene promoter construct operably linked to a CAT reporter gene containing the sequences that lie between -1257 and -353 of c-myc promoter (abstract, page 281; page 287, left

column, lines 19-21) to electromagnetic fields of 8μT and 60 Hz (page 283, right column, bottom paragraph).

The presence of eight nCTCTn sequences is an inherent property of the –1257 to –353 c-myc promoter region. The intended use of the claimed composition is given patentable weight when making a determination of patentability under 35 U.S.C. 102 only when it serves to define a structural requirement. The intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. Furthermore, the preamble is generally nonlimiting if it merely recites an inherent property. See MPEP 2111.02. In the instant case, the prior art structure has all the features required to perform the intended use recited in the claims. The claiming of a new use, new function, or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best* 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). See also MPEP 2112.

Thus, Lin et al. (1994) anticipated the invention of claims 1, 5-8, 9, 11, 12.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 8-10, 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Han et al. (1998, Journal of Cellular Biochemistry vol. 71, pages 577-583) and Lin et al. (1994, Journal of Cellular Biochemistry vol. 54, pages 281-288).

Although the method of the invention is not enabled for gene therapy, the method itself and the EMRE elements from c-myc promoter and hsp70 promoter are disclosed in the prior art. And the claims do not require that the constructs be introduced into an animal.

Han et al. teach a method of gene regulation by inducing the hsp70 promoter using magnetic fields of 8μT and 60 Hz (page 578, right column, 'magnetic field exposure conditions") wherein the region in the hsp70 promoter responsive to magnetic fileds mapped to a domain between –230 and –160 in the promoter (page 581, left column, bottom paragraph).

The presence of three nCTCTn sequences within this domain is an innate property of this sequence. The intended use of the claimed composition is given patentable weight when making a determination of patentability only when it serves to define a structural requirement. The intended use must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. Furthermore, the preamble is generally nonlimiting if it merely recites an inherent property. See MPEP 2111.02. In the instant case, the prior art structure has all the features required to perform the intended use recited in the claims. The claiming of a new use, new function, or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best* 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). See also MPEP 2112.

Han et al. do not teach the induction of gene expression by introducing EMREs into a gene promoter not having any EMREs. However, Han et al. teach that the stress response proteins induced by magnetic fields provide cytoprotection (pages 580 and 581, bridging sentence) from both lethal temperatures and anoxia and provide the motivation for using the method for stimulating genes that have a protective effect.

Lin etal (1994, Journal of Cellular Biochemistry vol. 54, pages 281-288) teach a method of gene regulation by introducing c-myc gene promoter construct that contains EMREs that lie between -1257 and -353 of c-myc promoter (abstract, page 281; page 287, left column, lines 19-21) operably linked to a CAT reporter gene and exposure of the construct to electromagnetic fields of 8μT and 60 Hz (page 283, right column, bottom paragraph). Thus, Lin et al. (1994) provide the motivation for the use of their method to induce heterologous genes which are otherwise not responsive to EM field induction.

Therefore, one of ordinary skill would have been motivated to use the hsp70 EMREs of Han et al. in the method of Lin et al. and induce genes that do not otherwise respond to EM field exposure. The motivation to do so and the expectation of success were derived from the teachings of Lin et al. (1994) who successfully demonstrated that EMREs can be introduced upstream of genes to be induced that do not otherwise respond to EM field exposure due to lack of EMRE elements in their promoter region.

Therefore, the claimed method would have been prima facie obvious to one of skill at the time of the invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sita S Pappu whose telephone number is (703) 305-5039. The examiner can normally be reached on Mon-Fri (8:30 AM - 5:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on (703) 305 1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308 4242 for regular communications and (703) 872 9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Tracey Johnson, whose telephone number is (703) 305-2982.

Anne-marie Baker
ANNE-MARIE BAKER
PATENT EXAMINER

S. Pappu
June 28, 2002